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S100A8 和 S100A9 在冠心病中的研究进展

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[关键词]　S100A8；　S100A9；　动脉粥样硬化；　急性冠状动脉综合征

[摘　要]　S100A8 和 S100A9 作为内源性危险相关分子模式与 Toll 样受体 4 和晚期糖基化终产物受体相识别，通过参与免疫应答，改变内皮通透性并促进斑块内炎症，从而影响动脉粥样硬化的发生和发展。此外，S100A8 和 S100A9 血浆水平升高与增加心血管事件的风险密切相关。本文综述 S100A8 和 S100A9 的研究现状及其在冠心病的预防、治疗及预后评估中的应用前景。

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Research progress of the relationship between S100A8 and S100A9 and coronary heart disease

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[**KEY WORDS**]　S100A8;　S100A9;　atherosclerosis;　acute coronary syndrome

[**ABSTRACT**]　S100A8 and S100A9, as endogenous risk-associated molecular patterns, recognize Toll-like receptor 4 and advanced glycation end product receptors, participate in immune response, change endothelial permeability and promote inflammation within the plaque, which affects the development of atherosclerosis.　In addition, the elevated plasma levels of S100A8 and S100A9 are associated with an increased risk of future cardiovascular events.　This article reviews the research status of S100A8 and S100A9 and their application prospects in the prevention, treatment and prognosis evaluation with coronary heart disease.

S100A8 和 S100A9(S100A8/S100A9)属于 S100 钙蛋白家族成员，通常以异二聚体形式存在[1]。这些蛋白主要依赖于髓样细胞性炎症和自身免疫状态而大量表达，在细胞内 S100A8/S100A9 参与炎性细胞的迁移和花生四烯酸(arachidonic acid，AA)的代谢，在细胞外促进中性粒细胞、单核细胞募集和细胞因子分泌[2]。S100A8/S100A9 血浆水平升高预示未来心血管事件的发生率升高。本文就 S100A8/S100A9 的研究现状及其在冠心病的预防、治疗及预后评估中的应用前景作一综述。

1　S100A8 和 S100A9 的分子基础及来源

S100 蛋白是钙结合蛋白家族中的一个亚族。因这些蛋白均含有“EF-手”结构，该结构与带电荷的氨基酸共享一个共同的螺旋-环-螺旋基序，因此具有较高的 Ca^{2+} 亲和力[3]。目前，在脊椎动物中有超过 20 个低相对分子质量(10～14 kDa)S100 蛋白被发现[4]，其中 S100A8/S100A9 属于其中一员，两者都具有两个“EF-手”结构，在体内可形成同二聚体和异二聚体，通常以异二聚体的形式发挥作用[1]。S100A8/S100A9 多在髓系相关细胞内表达，如单核细胞、中性粒细胞、巨噬细胞，所以也称髓样相关蛋白(myeloid-related protein，MRP)8 和 14[5]，此外，S100A8/S100A9 在响应相关应激刺激时，也可在非髓系细胞中表达。在生理情况下，内皮细胞、血管平滑肌细胞、血小板中几乎检测不到 S100A8/S100A9，但若用脂多糖(lipopolysaccharide，

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LPS)、白细胞介素 1β(interleukin-1β, IL-1β)或肿瘤坏死因子 α(tumor necrosis factor-α, TNF-α)活化之后,内皮细胞和血小板内则出现表达[6]。从完整非髓系细胞释放的 S100A8/S100A9 显著低于从髓样细胞释放的 S100A8/S100A9,表明这些非髓系细胞表达的 S100A8/S100A9 的生物学效应可能主要在细胞内。而血小板和髓样细胞表达的 S100A8/S100A9 通常分泌到循环中发挥生物学效应,如调节血管平滑肌细胞增殖、单核细胞迁移以及关键细胞因子的产生[7-8]。

2 生物学功能

2.1 细胞内功能

因 S100A8/S100A9 与 Ca^{2+} 的特殊亲和性,所以作为细胞内 Ca^{2+} 传感器参与调节 Ca^{2+} 依赖性信号传导。S100A8/S100A9 介导细胞骨架的快速重排,这是促进细胞迁移和吞噬作用的先决条件。S100A8/S100A9 在吞噬细胞中的微管聚合和稳定中起重要作用,S100A8 直接与微管蛋白结合,而 S100A9 充当调节因子,S100A9 通过 Ca^{2+} 和 p38 丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路实现磷酸化逆转微管形成并导致细胞骨架重排,从而引起白细胞迁移[9]。Ca^{2+} 与 S100A8/S100A9 中每个"EF-手"的结合是之后 AA 结合的先决条件。S100A8/S100A9 将 AA 转运至膜后结合 gp91phox 亚基会促进还原型烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate, NADPH)氧化酶的活化,从而使吞噬细胞产生活性氧[10]。S100A8/S100A9-AA 复合物可被炎症灶处的浸润细胞内化,以合成炎症介质,如白三烯,引起白细胞脱颗粒以及损伤血管内皮,从而促进炎症的发生和反馈调节[11]。

2.2 细胞外功能

体内外实验表明,S100A8/S100A9 对吞噬细胞均具有强大的趋化活性,S100A9 可以驱动粒细胞集落刺激因子的合成,调节中性粒细胞的趋化性[12]。异二聚体 S100A8/S100A9 能促进中性粒细胞表面 CD11b 蛋白表达,增加中性粒细胞蓄积[13]。除了趋化功能,S100A8/S100A9 还通过上调内皮细胞表面黏附分子表达增强吞噬细胞与内皮细胞的相互作用促进吞噬细胞迁移。而且,S100A8/S100A9 也影响内皮细胞间的连接而增强血管通透性,促进单核细胞和巨噬细胞跨内皮迁移[14-15]。

S100A8/S100A9 可以诱导炎症细胞中多种细胞因子分泌,从而维持并加剧炎症。S100A8/S100A9 可以介导 Toll 样受体 4(Toll-like receptor 4, TLR4)/MyD88/核因子 κB(nuclear factor-κB, NF-κB)炎症信号通路激活,引起促炎细胞因子 TNF-α 和 IL-1β 分泌[16]。此外,还可通过与晚期糖基化终产物受体(receptor for advanced glycation end products, RAGE)结合导致 MAPK 磷酸化和 NF-κB 活化,引起心肌功能障碍和缺血后心衰[17-18]。在生理和病理状态下,S100A8 和 S100A9 的功能较复杂,通常两者被认为可以促进炎性反应,但也有研究揭示其抗炎和免疫调节功能[19]。

3 S100A8/S100A9 与动脉粥样硬化

近年来,嗜中性粒细胞和 S100A8/S100A9 参与心血管疾病引起了越来越多的关注。S100A8/S100A9 存在于小鼠和人类的动脉粥样硬化斑块中[20-21]。高血糖导致骨髓中单核细胞和中性粒细胞增多,这些细胞分泌的 S100A8/S100A9 与 RAGE 相互作用,导致炎症性 Ly6-C hi 单核细胞释放,进而持续加重动脉粥样硬化[22]。若 RAGE 缺乏,则会延迟斑块进展和减弱血管炎症,此外若缺乏 S100A8/S100A9 受体 TLR4 或下游 MyD88 时,$ApoE^{-/-}$ 高脂饮食小鼠斑块明显减小[23]。在糖尿病患者和小鼠的动脉粥样硬化斑块中,过表达 RAGE, S100A8/S100A9 的生物学效应增强[24]。若抑制 S100A8/S100A9 与 RAGE 的结合,S100A8/S100A9 的作用被抑制[25],这些研究表明 RAGE 和 TLR4 及其配体 S100A8/S100A9 在加速动脉粥样硬化发展中起着重要作用。此外,特异性敲除 S100A9,可使血小板表面 P-选择素表达减少,从而减少白细胞积累和动脉粥样硬化斑块面积[8]。临床研究证明血浆 S100A8/S100A9 和冠状动脉疾病(coronary artery disease, CAD)的类型和严重程度呈正相关[26]。人颈动脉斑块免疫组织化学和生物化学分析表明,S100A8/S100A9 的含量较高,有大量巨噬细胞浸润,胶原蛋白含量低以及炎性因子和基质金属蛋白酶的浓度升高,此外在不稳定性斑块中 S100A8/S100A9 阳性的巨噬细胞数量增加[27]。

4 S100A8/S100A9 与急性冠状动脉综合征

S100A8/S100A9 与急性 CAD 事件发生率之间的关联已逐渐明确,与稳定型心绞痛或经血管造影

评估的正常冠状动脉的个体相比,急性冠状动脉综合征(acute coronary syndrome,ACS)患者在缺血事件中血浆 S100A8/S100A9 水平明显升高[28]。缺血的心肌细胞不表达 S100A8/S100A9[29],S100A8/S100A9 可能从募集到损伤部位的活化单核细胞和嗜中性粒细胞释放。与全身循环相比,S100A8/S100A9 在冠状动脉闭塞部位明显增加[15]。此外,血浆 S100A8/S100A9 水平在 ACS 出现症状后的 3 h 即出现升高,相较于肌钙蛋白或肌红蛋白等心肌损伤的经典指标更加敏感[15]。然而,S100A8/S100A9 对于心肌梗死的诊断较差[30]。血小板 mRNA 的微阵列和反转录聚合酶链反应分析显示,与稳定型心绞痛患者相比,ST 段抬高型心肌梗死患者 S100A9 mRNA 水平显著升高[15]。当出现 ACS 时,巨核细胞可能对机体内的可溶性蛋白信号做出响应。由于血小板来源于巨核细胞,循环血小板的 RNA 谱反映了骨髓巨核细胞中的这种变化[15]。

有研究显示抑制 S100A9 与 CD36 的信号传导可抑制血栓形成而不影响止血,有研究[31]利用该特性,在 S100A9 中选择了合适的区域作为靶点,构建针对 S100A9 的疫苗。S100A9 疫苗在血栓性大脑中动脉阻塞实验中的结果显示,实验组动物大脑中动脉闭塞时间明显延长,且与氯吡格雷作用类似,不会影响止血相关参数。S100A9 疫苗有效避免了传统抗血小板药物的不良反应,为预防心血管疾病提供一种新策略。此外,在心肌梗死小鼠模型中,降低 S100A9 可抑制炎症,并改善心脏功能。由于过量的 S100A8/S100A9 释放与突发性心力衰竭相关,因此降低 S100A9 可能是改善 ACS 患者预后的可行策略[32]。

5　小结与展望

S100A8/S100A9 在先天免疫、炎症、传统心血管危险因素和 CAD 之间的复杂调节中发挥重要作用。冠状动脉病变处聚集的活化嗜中性粒细胞和单核细胞是 S100A8/S100A9 的主要来源,S100A8/S100A9 可促使内皮细胞表达黏附分子,增加细胞间黏附,改变内皮通透性,同时使髓样细胞自身形成正反馈,不断加剧炎症反应。S100A8/S100A9 与动脉粥样硬化和缺血后心肌损伤有关,作为生物标志物可以反映亚临床颈动脉和冠状动脉斑块受损程度。在心肌缺血及心肌坏死时,血浆中 S100A8/S100A9 含量迅速增加,并与患者不良预后有着密切关系。S100A8/S100A9 有望成为 CAD 的临床生物标志物和治疗靶标。

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